REMARKS

Applicants have amended claims 9 and 21 and added new claims 27-29. Support for new claims 27 and 28 can be found at page 14, line 16, through page 15, line 12 of the specification. Support for new claim 29 can be found at page 18, lines 8-18 of the specification. No new matter has been introduced by the above amendments.

Claims 1-3, 6-11, and 20-29 are now pending. Reconsideration of this application, as amended, is requested in view of the following remarks.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 9, 20, and 24 are rejected as being indefinite. See the Action, page 3, lines 1-10. Applicants discuss the rejection of each claim below.

The Examiner asserts that the step "converting the resultant compound of formula (I) into a further compound of formula (I)" recited in claim 9 is indefinite, since it is unclear which compound is converted into which. See the Action, page 3, lines 4-6. Applicants have removed this step from claim 9 and recited a corresponding step in new claim 27, which depends claim 9. Claim 27 recites "converting the first compound of formula (I) into a second compound of formula (I)." "First compound" is a generic term used to denote the product of any one of the three reactions recited in claim 9. Claim 27 requires that the "first" compound (i.e., the product of one of the claim 9 reactions) be converted either into a pharmaceutically acceptable salt thereof, or into a second compound of formula (I) different from the first compound. Applicants believe that the intent of claims 9 and 27 is now clear.

The Examiner asserts that the term "IKK2 mediated disease" recited in claim 20 is indefinite since "it is unclear what the intended diseases are." See the Action, page 3, lines 7-8. Applicants are puzzled by this statement. The claim on its face clearly describes the intended diseases as "IKK2-mediated." The term "IKK2 mediated disease" refers to a disease in which IKK2 plays an important role in the disease's pathology, and so the disease can be treated by modulation of IKK2 enzyme activity. Several examples of IKK2-mediated diseases are listed in the specification. See page 18, lines 10-18.

Applicants do not understand why the Examiner believes this term to be indefinite. It is simply a category of conditions, much like "inflammatory diseases" or "infectious diseases" are categories of conditions. The fact that a category is broad and may even include diseases not yet discovered does not render it unpatentably indefinite under § 112, second paragraph.

Finally, the Examiner contends that multiple sclerosis is not an inflammatory disease. Based on this, he concludes that claim 24, which specifies that "the [inflammatory] disease is multiple sclerosis," is indefinite. This ground for rejection is not understood. Contrary to the Examiner's belief, it is well known that multiple sclerosis is indeed an inflammatory disease. See, e.g., Weiner et al. *Arch Neurol.* 2004; 61: 1613-1615 (the first paragraph) and the abstract of Catalaa et al. *Am. J. of Neuroradiology* 1999, 20: 1613-1618, copies of which are attached hereto as "Exhibit A." Clearly, the Examiner's rejection of claim 24 for indefiniteness is groundless.

For the reasons set forth above, Applicants ask the Examiner to withdraw these rejections.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 20 and 24 are rejected as not being enabled. The Examiner opines that "the specification, while being enabling for the treatment of an inflammatory disease, does not reasonably provide enablement for the treatment of other IKK2-mediated disease or multiple sclerosis." See the Action, page 3, lines 19-21.

Claim 20 covers a method for treating an IKK2-mediated disease by a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof. Claim 24 covers a method for treating a specific inflammatory disease, i.e., multiple sclerosis.

The Examiner asserts six grounds, i.e., **(1)** through **(6)**, to support the rejection. See the Action, page 4, line 13 to page 6, line 17. Applicants traverse each ground below.

(1) The breadth of the claims.

The Examiner indicates that "[s]aid method [of claim 20] covers the treatment of various diseases including: inflammatory diseases (e.g., rheumatoid arthritis, osteoarthritis, spondylitis, etc.), Reiters syndromes .... Thus, the scope of claim 20 is very broad." See the Action, page 4,

line 14 through page 5, line 2. Applicants agree that the scope is broad, but do not agree that the scope exceeds what Applicants have enabled. The diseases listed by the Examiner are all associated with IKK2. As indicated by the specification, "inhibition of IKK2 is beneficial" in these diseases. See page 18, lines 7-18. Since Applicants have described compounds that inhibit IKK2, it stands to reason that any IKK2-mediated disease may be amenable to treatment with the claimed compounds. The scope of claim 20 is perfectly aligned with what Applicants have enabled. The Examiner provides no evidence to the contrary.

The Examiner also indicates that since multiple sclerosis is not an inflammatory disease, "the scope of claim 24 cannot be practiced." See the Action, page 5, lines 3-6. The Examiner clearly errs. As pointed out above, multiple sclerosis is indeed an inflammatory disease.

(2) The amount of direction or guidance presented.

The Examiner asserts that "[t]he specification simply does not provide sufficient guidance for the treatment of many diseases that are presumably associated with IKK2." See the Action, page 5, lines 16-17.

Applicants do not agree. The specification provides an *in vitro* assay to evaluate efficacy of the claimed compounds in inhibiting IKK2 activity. See page 65, line 15, through page 66, line 8. The results of this assay are reasonably correlated to efficacy of treating any IKK2-mediated disease in which inhibition of IKK2 activity is beneficial. Any compound exhibiting high potency in the *in vitro* assay could then be tested in suitable animal models for the disease, or if no such animal model exists, in a clinical trial. Applicants are uncertain why the Examiner believes that one of ordinary skill in the art of testing drugs would not know how to do this.

The Examiner also contends that

> there is no evidence if such an activity could treat heart failure, Graves' disease, AIDS, cancer, psoriasis, multiple sclerosis, etc. ... there is no evidence that the claimed compounds can reduce blood glucose level, or lipid, or cholesterol ... there is no evidence that the claimed compounds can inhibit mitosis for the treatment of cancer or cancer metastasis, nor is there evidence for the inhibition of HIV replication necessary for the treatment of AIDS. The Action, page 5, lines 11-15.

The Examiner seems to be questioning whether Applicants' evidence that the claimed compounds possess IKK2-inhibitory activity is sufficient proof that these compounds will be useful in treating IKK2-mediated conditions other than inflammatory conditions. The fact that the Examiner accepts that Applicants' assertions are "reasonable" with respect to inflammatory conditions but rejects those assertions with respect to any other conditions suggests that he has focused on some aspect of the compounds (it is not clear what) other than their activity as IKK2 inhibitors. Applicants submit that the important point is the involvement of IKK2 in the etiology of the disease, and not whether the disease can be characterized as "inflammatory" or not. It is reasonable to expect IKK2 inhibitors to inhibit IKK2 activity regardless of what IKK2-mediated disease is involved. The Examiner has offered no logical basis for doubting this. Furthermore, Applicants note that many if not all of the listed conditions have an inflammatory component that the Examiner apparently does not recognize: for example, multiple sclerosis, asthma, psoriasis, Graves's disease, diabetes, and heart failure.

(3) The state of the prior art.

The Examiner asserts that "in the pharmaceutical art, no single compound can treat inflammatory disease, multiple sclerosis, heart failure, diabetes, asthma, cancer, AIDS, etc." See the Action, page 5, lines 18-19.

Applicants fail to see the pertinence of this assertion. It may well be that certain of the claimed compounds will prove more efficacious for certain IKK2-mediated diseases than for others, but that does not mean it is unreasonable to propose that IKK2 inhibitors as a class are generally useful to treat IKK2-mediated conditions. Furthermore, the examples the Examiner provides to support his point are at best of marginal relevance, and at worst simply inaccurate. First, while NSAIDs may not be useful against all conditions, they are certainly useful against many. Second, Applicants point out that some classes of drugs, such as steroids, are utilized to treat a wide range of conditions including both of the examples mentioned by the Examiner in the carryover sentence of pages 5-6: arthritis and asthma. Third, the Examiner's breathtakingly sweeping statement that "drugs that treat cancer cannot treat AIDS" is simply not true. One example of a drug commonly used to treat both AIDS and cancer is 5-fluorouracil. Fourth, some

anti-cancer drugs, such as cytokines, are specifically intended to stimulate the patient's own immune system to fight the cancer, so would not "suppress the immune system" as the Examiner supposes must be true of all anti-cancer agents. Indeed, interferon alpha is one cytokine that has been used to treat both AIDS and cancer.

The above examples are provided merely to correct the Examiner's apparent misconceptions about the broad usefulness of some drugs. If a given cellular mechanism is at the basis of multiple medical conditions, then it is quite conceivable that a compound that inhibits that mechanism will have broad applicability to many if not most of those conditions. This is a more reasonable way to look at the issue than simply to deny that such is possible, with no sound evidence.

(4), (5), and (6) The skill of those in the art, the predictability of the art and the quantity of experimentation necessary.

The Examiner asserts that "the *in-vitro* activity does not always warrant the same *in-vivo* activity." Based on that, he concludes that "a mere showing of the *in-vitro* inhibition of IKK2 does not sufficiently guide the skilled clinician to treat various diseases that are presumably related to IKK2." See the Action, page 6, lines 11-14. Applicants disagree.

As mentioned above, it is logical to assume a correlation between efficacy of inhibiting IKK2 and efficacy of treating IKK2-mediated diseases. The Examiner has marshalled no evidence to contradict this simple logic. The *in vitro* assay provided in the specification describes testing efficacy of the claimed compounds in inhibiting IKK2 activity. The results can be used to predict efficacy of treating IKK2-mediated diseases. Thus, the *in vitro* assay provides adequate guidance for the treatment of IKK2-mediated diseases with the claimed compounds.

The Examiner indicates that

> treating various diseases using a single class of compounds does not conform to the standard practice of medicine. Thus, it would require undue experimentation for the skilled clinician to treat multiple sclerosis and other IKK2 related diseases. See the Action, page 6, lines 14-17.

Again, the Examiner's view of the "standard practice of medicine" does not comport with reality. As discussed above, there are many examples where a single class of compounds is used

to treat "various diseases," even seeming disparate ones. The key is that a similar mechanism affected by the drug underlies all of the "various diseases." Applicants are not claiming that the IKK2 inhibitors of the invention can be used to treat all diseases. Rather, Applicants have limited claim 20 to treatment of those diseases that reasonably could be treated with IKK2 inhibitors: i.e., IKK2-mediated diseases. Applicants do not understand why the Examiner does not believe it is reasonable to treat IKK2-mediated diseases with IKK2 inhibitors, nor why he maintains this would involve undue experimentation. As the Examiner is no doubt aware,

> [a] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC 1988), citing *In re Jackson*, 217 USPQ 804, 807 (CCPA 1969).

To determine whether a claimed compound can be used to treat an IKK2-mediated disease, a skilled person would first test the compound in the *in vitro* assay described in the specification. If it exhibits good efficacy in inhibiting IKK2 activity, the skilled person would test the compound on an animal model of the disease of interest. The techniques required for such tests were well known at the time the invention was made. They are mere routine procedures within the skill of a skilled person in this field. Applicants fail to understand why the Examiner believes that testing the claimed compounds against any of the listed IKK2-mediated conditions would be any more difficult than testing any given compound against any given condition. The techniques are routine in the art, once activity in the *in vitro* assay is established as taught in the specification.

Accordingly, Applicants submit that the specification provides adequate enablement for the claimed invention. Withdrawal of the rejection is respectfully requested.

Applicants ask that all pending claims be allowed.

Enclosed is a $1020 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney's Docket No. 06275-233001.

Respectfully submitted,

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